

### **REMARKS**

Please enter this Amendment and Response and reconsider the rejection of the claims.

Applicants add new claims 53-65. The new claims are supported throughout the specification including at original claim 11; page 11, lines 18-21; page 11, lines 25-27, page 11, lines 32-35; page 12, lines 9-11; page 19, line 29 to page 20, line 1; page 29, lines 30-32; and page 30 lines 26-27.

### **INTERVIEW SUMMARY**

Applicants thank Examiner Blanchard for the interview conducted on August 1, 2006. We discussed 112 issues with regard to claim 25.

### **OBJECTION TO THE SPECIFICATION**

The Examiner objected to the specification for referring cys-pro-pro-cys by “CPC” instead of “CPPC”. While not acquiescing to the Examiner’s statements, Applicants have amended the specification to refer to “CPPC” at page 29, lines 32-33. Applicants request withdrawal of this rejection.

### **35 U.S.C. § 112, FIRST PARAGRAPH**

The Examiner rejected claims 25, 29, 39, 43-44 and 49-52 under 35 U.S.C. § 112, first paragraph, written description. The Examiner contends the specification lacks support for the language in claim 25, 44, and 49. The language that the examiner contends lacks support is “an amino acid sequence of up to 10 amino acids, wherein the amino acid sequence of about up to 10 amino acids comprises a C terminal amino acid sequence of Cys-Ala-Ala”. Applicants respectfully traverse.

Applicants note that there is a strong presumption that an adequate written description of the claimed invention exists. (See MPEP 2163.II.A.) To adequately describe the claims, the specification need not describe *ipsis verbis* what is recited in the claims; rather, the claim limitations may be supported in the specification through implicit or inherent disclosure rather than express disclosure. (MPEP 2163 I.B.) Even if

the specification does not explicitly recite a claim limitation, sufficient written description exists for the limitation if one of skill in the art can "immediately discern the limitation" from reading the original specification. *Waldemar Link, GmbH & Co. v. Osteonics Corp.*, 31 USPQ2d 1855 (Fed Cir. 1994). "If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met." (MPEP 2163 II.A.3(a).) If the specification contains a description of the invention, although not *ipsis verbis*, then the Examiner must provide reasons why one of skill in the art would not consider the description sufficient. In *Re Alton*, 76 F3d 1168 (Fed. Cir. 1996). In light of the foregoing standards, the present claims are clearly adequately described by the specification.

Applicants' claim 25 is directed to a composition comprising a monospecific  $F(ab')_2$ , wherein the  $F(ab')_2$  comprises a first and second Fab' each comprising a CH1 domain fused to an amino acid sequence of up to 10 amino acids, wherein the amino acid sequence of up to 10 amino acids comprises a C terminal amino acid sequence of Cys-Ala-Ala. Applicants' claim 49 is directed to a composition comprising a Fab' coupled to a heterologous molecule, wherein the Fab' comprises a CH1 domain fused to an amino acid sequence of up to 10 amino acids, wherein the 10 amino acid sequence comprises a C terminal amino acid sequence of Cys-Ala-Ala.

As an initial matter, Applicants disagree with the Examiner's characterization of the support in the specification for the claimed subject matter. The examiner contends that there is only one location in the specification that describes a polypeptide of 10 amino acid residues. Applicants respectfully disagree. As described below, Applicants submit that there are many places in the specification describing cysteine containing polypeptides that have up to 10 amino acids. For example, Applicants indicate that the cysteine containing polypeptide can be a hinge region sequence variant containing a single free thiol cysteinyl residue. See the specification at page 6, lines 24-29. The specification further indicates that a Fab amino acid sequence can be modified by deleting or substituting all of the hinge region cysteines C terminal to the first cysteine. See the specification at page 7, lines 25 to 31. Since the sequences of the hinge regions

were known, one of skill in the art would understand that a Fab amino acid sequence with deletions of all of the hinge region cysteine residues C terminal to the first cysteine of the hinge region of at least an IgG1, IgG2 and IgG4 antibody would have about 10 amino acids or less. Moreover, in the working example, Applicants teach that the CH1 domain of hu Mab4D5 was extended to encode part of the IgG1 cysteine containing hinge region of the antibody but not the full length hinge sequence. See the specification at page 29, lines 30-32. Thus, Applicants submit the specification describes and supports polypeptides fused to a CH1 domain of up to 10 amino acids in more than one location.

Secondly, the examiner contends that the specification only supports direct fusion of the polypeptide sequence Cys-Ala-Ala. Applicants respectfully submit that the Examiner is improperly reading the phrase “directly fused” into the specification because, first and foremost, this phrase does not appear in the specification. Applicants submit one of skill in the art reading the specification would understand that that the claimed subject matter is not limited to direct fusion. The specification does indicate that in some embodiments, the CH1 sequence is fused to the sequence Cys-X-X, wherein X is Ala, Arg, Asp, or Pro. However, this language does not require direct fusion and other description in the specification and claims provide evidence that Applicants’ specification does not only describe direct fusion. For example, original claim 11 refers to a Fab’ comprising a C terminal amino acid sequence Cys-Ala-Ala. The specification further describes that a Fab’ variant with a single hinge cysteine residue was made having a C terminal amino acid sequence Cys-Ala-Ala. See page 30, lines 26-27. Page 6, lines 24-27 of the specification indicates that the polypeptide sequence fused to the CH1 domain may comprise only the cysteinyl residue or can be present in a polypeptide. As discussed above, the polypeptide fused includes, for example, the Fab amino acid sequence modified by deleting or substituting all of the hinge region cysteines C terminal to the first cysteine. See page 7, lines 26-27. In the working example, Applicants teach that the CH1 domain of huMab4D5-8 was extended to encode part of the cysteine containing hinge sequence. See page 29, lines 30-32. Thus, one of skill in the art reading the specification would understand that the Fab’ variants were made by including at least a portion of the hinge region and including a C terminal amino acid sequence of, e.g. CPPC

or CAA. Thus, applicants submit the examiner has improperly imported the word directly into the claims and the specification.

Applicants further support this contention with Carter et al., *Biotechnology*, 10:163 (1992). The Carter et al reference, co-authored by the inventor of the instant application, shows that the Fab' comprising a C terminal Cys-Ala-Ala sequence included a portion of the hinge region sequence. Figure 2 of the paper shows that the sequence C terminal to the CH1 domain includes the sequence DKHTHTCAA with the sequence DKTHT corresponding to part of the IgG1 hinge region sequence. These results are consistent with the language in the specification indicating a part of the hinge region was included but modified.

Applicants submit that the specification describes many species that support the genus of a polypeptide of up to 10 amino acids that comprises a C terminal amino acid sequence such as Cys-Ala-Ala. As discussed above, Applicants have described many different types of such polypeptides including a Fab amino acid sequence having all hinge region cysteines deleted or substituted C terminal to the first cysteine of the hinge region. See the specification at page 7, lines 25 to 31. Since the sequences of the hinge regions were known, one of skill in the art would understand that deletion of the hinge region cysteine residues C terminal to the first cysteine for at least IgG1, IgG2 and IgG4 antibodies would have about 10 amino acids or less. In the working example, Applicants teach that the CH1 domain was extended to encode part of the IgG1 hinge but not the full length hinge sequence and that one such Fab' variant has a C terminal amino acid sequence Cys-Ala-Ala. See page 29, lines 30-32 and page 30, lines 26-27. Fab' variants having or comprising a C terminal amino acid sequence Cys-Ala-Ala were described throughout the specification and in the originally filed claims. The specification identifies the known hinge region sequences as one possible source of such polypeptide sequence. Other sources of cysteine containing polypeptides include peptides from other known polypeptides that contain at least one cysteine such as immunoglobulins, carrier proteins, growth factors, receptors and the like. Thus, Applicants submit the specification provides written description for the claimed subject matter.

Based on the foregoing, Applicants request withdrawal of this rejection.

**INTERVIEW REQUEST**

Applicants' request an interview with the examiner and his supervisor to discuss any outstanding issues.

**SUMMARY**

Applicant submits the claims are in condition for allowance and notification to that effect is earnestly solicited. Applicant requests that the Examiner contact Applicant's representative if prosecution may be assisted thereby.

Respectfully submitted,

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